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| 09/991,681 | 11/26/2001 | Patricia A. Billing-Medel | 6084.US.D1 | 4490 |

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| EXAMINER | |
|---|---|
| DAVIS, MINH TAM B | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/991,681 | BILLING-MEDEL ET AL. | |
| | Examiner | Art Unit | |
| | MINH-TAM DAVIS | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 17-19 are being examined.

The following are the remaining rejections.

## REJECTION UNDER 35 USC 101, UTILITY

Rejection under 35 USC 101 of claims 17-19 pertaining to lack of a specific, substantial asserted utility or a well established utility remains for reasons already of record in paper No.7.

Applicant asserts that Example 1, page 54 of the specification that the consensus sequence (SEQ ID NO:10) encoding SEQ ID NO:27 is prostate specific, and is found greater than 12 times more often in prostate than non-prostate tissue, using InCyte LIFESEQ database, as disclosed in WO95/206681 . Applicant asserts that therefore, the specification teaches the involvement of SEQ ID NO:27 with the etiology of prostate diseases.

This argument is found not to be persuasive. Being specific for prostate cancer tissue as compared to normal non-prostate tissues does not confer any information concerning the involvement of SEQ ID NO:27 with the etiology of prostate diseases, such as prostate cancer, nor any specific utility, because it does not show that SEQ ID NO:27 is involved with or responsible for the development of prostate diseases, such as prostate cancer, and thus SEQ ID NO:27 cannot be used in detecting or treating

prostate diseases, based solely on being specific to prostate tissue (see further discussion below).

Further, it is unpredictable whether SEQ ID NO:27 or the encoding polynucleotide of SEQ ID NO:10 is actually overexpressed in prostate cancer tissue as compared to normal non-prostate tissues because it is questionable that the data using InCyte LIFESEQ database, as disclosed in WO95/206681 is reliable. It seems that some of Incyte's libraries could be underrepresentative of all mRNAs in a cell, based on the data in WO 95/20681, having as Applicant Incyte Pharmaceuticals, Inc. It is known that cells in the human body seem to have approximately 100,000 genes and the differences among different types of cells are believed to reflect the differential expression of the 100,000 or so genes (WO 95/20681, p.2, last paragraph). Further, a typical conventional cDNA library should have a clone complexity of at least $10^6$ clones (WO 95/20681, p.4, lines 33-35). However, the representative population of the Incyte gene transcript libraries seems to range from about 7,000 to about 20,000 clones (Table 2 on page 43, first four lines, Table 4 on page 46, first four lines). Thus it is clear that not all of the 100,000 or so genes is represented. It is noted that from screening underrepresented libraries, a polynucleotide that is not expressed in one library or is expressed in another appears to be an artifact of the analytical system and cannot be extrapolated to a prediction of whether that the polynucleotide is expressed in the tissue "represented" by the library. Thus it is questionable whether SEQ ID NO:10, encoding SEQ ID NO:27 is overexpressed in prostate cancer tissue, as compared to non-prostate normal tissue.

Moreover, even if the encoding polynucleotide sequence of SEQ ID NO:10 is overexpressed in prostate tissue as compared to normal non-prostate tissues, it cannot be extrapolated to the expression of the encoded polypeptide of SEQ ID NO:27, because there is no correlation between the level of expression of mRNA and that of the corresponding encoded polypeptide. For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Further, Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Thus based on the teaching in the art, and in the specification, one cannot predict that SEQ ID NO:27 is actually overexpressed in prostate cancer tissue as compared to normal non-prostate tissues

Applicant asserts that the Examiner has focused on the single utility of natural expression of the claimed sequences. Applicant asserts that the claimed polypeptide has more than one specific utility. Applicant asserts that the claimed polypeptide may be useful for producing novel polypeptides that do not exist in nature, such as partial polypeptides, which may be useful as reagents in detecting prostate diseases. Applicant asserts that such reagents could be used to monitor for the elevated expression of such

marker in inappropriate body compartment, i.e. outside of the prostate, wherein identification of such expression outside of the normal host tissue would indicate prostate diseases. Applicant recites as an example, the well known prostate specific antigen PSA marker, which has similarly been used for detecting prostate cancer.

This argument is not found to be persuasive. Contrary to Applicant assertion, the Examiner did not focus on any single expression utility. The Examiner stated that SEQ ID NO:27 does not have any specific or substantial utility, because one cannot determine that SEQ ID NO:27 could be used for detecting prostate diseases, due to lack of information such as overexpression of SEQ ID NO:27 in prostate cancer tissue versus normal prostate tissue control, and further because one cannot determine that SEQ ID NO:27 could be used for treating prostate diseases, such as prostate cancer, in view of the absence of objective evidence that SEQ ID NO:27 is effective in treating prostate diseases, such as prostate cancer, and in view that cancer treatment is unpredictable, as taught by Gura, Jain, Curti, and Hartwell, all of record.

Moreover, different from PSA, which is overexpressed in serum in prostate cancer as compared to normal control, there is no indication that SEQ ID NO:27 is overexpressed in any bodily fluid, or in any tisues other than prostate tissues, in any diseases, as compared to normal control. Thus based on the teaching in the specification, one cannot determine that the claimed SEQ ID NO:27 could be used as reagents for detecting prostate diseases, such as prostate cancer. In addition, the contemplated detection of markers, the expression of which is elevated in inappropriate body compartment, is yet to be determined. "Congress intended that no patent be

granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPO at 696. Because of this, the claimed SEQ ID NO:27 does not have specific and substantial utility.

Applicant recites Bitran et al, MRCPath et al, Gamble et al, which teach the use of tissue specific tumor markers for detecting metastatic cancers. Applicant asserts that thus the claimed polypeptide could be used for detecting metastatic cancer.

The recitation of Bitran et al, MRCPath et al, Gamble et al is acknowledged and entered.

This argument is not found to be persuasive, because it is unpredictable that SEQ ID NO:27 could be used to detect metastatic prostate cancer cells, outside of the primary prostate cancer. It is unpredictable that metastasized prostate cells still express the claimed sequences, in view that expression of a sequence could be lost during the progression toward metastasis. For example, Kibel, AS et al, 2000, J urol, 164(1): 192-6 teach that gene expression in the chromosomal region 12p12-13 is different in primary and metastatic prostate cancer cells, and that inactivation in the chromosome region 12p12-13 occurs prior to metastasis. Zhau, HE, 1994, J Cell Biochem, Suppl 19: 208-216, teach expression of various biomarkers associated with prostate cancer progression. Zhau et al teach that in prostate cancer, PC-3N35 subclones which are cloned from primary and metastatic sites (lymph node, kidney and bone), show difference in the levels of protein expression of various markers, such as c-erbB, vimentin, ICAM-1, cytokeratin, collagen IV between the parental PC-3N35 clone and its metastatic subclones (p.209 and table 1) and that the subline derived from the

metastatic site lymph node has a 12p:17q translocation, whereas the bone-derived subline contains an isochromosome 7q (p.211, first column, first paragraph). Cheung S T et al, 2002, Cancer Research, 62(16): 4711-21, teach that from 63 metastatic clones, 39 known genes and 24 express sequence tags are down-regulated, whereas in other 27 metastatic clones 14 known genes and 13 express sequence tags are up-regulated. Ren, C et al, 1998, Cancer Res, 58(6): 1285-90, teach a loss of expression of lysyl oxidase mRNA during progression to metastasis. Gingrich, JR et al, 1996, Cancer res, 56(18): 4096-4102 teach a loss of normal E-cadherin expression as primary tumors become less differentiated and metastasize.

Thus in view of the above, one would not have expected that the claimed sequences are useful for diagnostic and prognostic information about the presence in a subject of an invasive prostate tumor.

Applicant asserts that concerning the unpredictability of cancer therapy, or gene therapy, the failure of thousands of potential cancer agents does not render the disclosed anticancer agents ineffective, because they are derived from a specific gene.

This argument is not found to be persuasive, because since cancer therapy and gene therapy is unpredictable, in the absence of objective evidence, one cannot determine that the claimed SEQ ID NO:27 or the encoding polynucleotide would be effective in cancer treatment or treating of diseases by gene therapy. Whether SEQ ID NO:27 is from a gene that is specific for the prostate tissue is not germane to the unpredictability of the effectiveness of SEQ ID NO:27 in treating diseases, such as prostate cancer.

Applicant asserts that the claimed polypeptides are useful for determining protein complexes and finding antibodies, and ultimately other markers specific for prostate tissue diseases. Applicant argues that a novel nut that may not be significanat by itself, but is significant in the functioning of a machine which performs a larger task, would still considered to have a specific utility.

This argument is not found to be persuasive, because other markers specific for prostate tissue diseases, based on screening using the claimed SEQ ID NO:27, are yet to be found. In the absence of any disclosed relationship between the claimed polypeptide and any disease or disorder and the lack of any correlation between the claimed polypeptide with any known disease or disorder, any information obtained from a screening assay would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPO at 696.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide. Because the claimed invention is not supported by a specific and/or well established utility for the reasons set forth, credibility of any utility cannot be assessed.

**REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT**

Rejection under 35 USC 112, first paragraph of claims 17-19 pertaining to lack of support by specific, substantial asserted utility, or a well established utility remains for reasons already of record in paper No.7.

The same arguments and answers in 101, utility rejection apply here as well.

**REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION**

Rejection under 35 USC 112, first paragraph of claims 17-19 pertaining to lack of a clear written description of a polypeptide "comprising" SEQ ID NO:28-31, remains for reasons already of record in paper No.7.

Applicant argues that the sequence is of relevant with respect to structure as well as function, since they carry information relating to epitopes, which would be relevant to the binding of substrates and therefore useful as markers for other molecules.

Applicant's arguments have been considered but are not deemed to be persuasive for the following reasons:

Due to the language "comprises", the claims encompass undisclosed sequences, with unknown structure, which are attached to the claimed fragment consisting of SEQ ID NO:28, 29, 30, or 31. The claims do not meet the Lilly requirement, because no representative species of the genus polypeptides comprising undisclosed sequences, with unknown structure, which are attached to the claimed fragment consisting of SEQ ID NO:28, 29, 30, or 31 is disclosed in the specification.

Further, contrary to Applicant arguments, there is no correlation between structure and function as epitopes of the polypeptides comprising SEQ ID NO:28-31,

because the epitopes or conformation of SEQ ID NO:28-31, when attached to undisclosed sequences, with unknown structure, are not disclosed in the specification, and because the conformation of SEQ ID NO:28-31, when attached to undisclosed sequences, with unknown structure, could be significantly affected by the attached unknown sequences. It is well known in the art that an epitope could be linear or conformational. Herbert et al, The Dictionary of Immunology, Academic Press, 4th edition, 1995, p.58, define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. Further, Bowie et al (Science, 1990, 247: 1306-1310, especially columns 1-2, p.1306) teach that the ability of proteins to fold into unique three-dimensional structures depends on the amino acid composition of the protein, and that certain positions in the sequence are critical to the three dimensional structure/function relationship. Roger, I et al, 1988, Bioscience Reports, 8(4): 359-368, teach that several epitopes of p85 glycoprotein are conformational determinants and are destroyed by reduction of said glycoprotein (abstract). Based on the teaching in the art, it is expected that the amino acids that are attached to SEQ ID NO:28-31, could have important influence in shaping the conformation of the epitope comprising SEQ ID NO:28-31. Thus because the conformation of the epitopes is not disclosed and could vary, dependent on the structure of the unknown sequences attached to SEQ ID NO:28-31, there is no correlation between structure and function as epitopes disclosed for the claimed polypeptides comprising SEQ ID NO:28-31.

**REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE**

Rejection under 35 USC 112, first paragraph of claims 17-19, while being enabled for a polypeptide consisting of the amino acid sequence of SEQ ID NO:28, 29, 30, or 31, but lack of enablement for a polypeptide "comprising" the amino acid sequence of SEQ ID NO:28, 29, 30, or 31, remains for reasons already of record in paper No.7.

Applicant asserts that the sequences contain important epitopes. Applicant reiterates that the claims are drawn to a product and not a specific method of use.

Applicant's arguments set forth in paper of 02/17/04 have been considered but are not deemed to be persuasive for the following reasons:

Due to the language "comprises", the claims encompass undisclosed sequences, with unknown structure, which are attached to the claimed fragment consisting of SEQ ID NO:28, 29, 30, or 31. Applicant has not taught how to make the claimed polypeptides comprising the amino acid sequences of SEQ ID Nos: 28-31.

Concerning the epitopes of the polypeptides comprising the amino acid sequences of SEQ ID Nos: 28-31, it is expected that the amino acids, that are attached to SEQ ID NO:28-31, could have important influence in shaping the conformation of the epitope comprising SEQ ID NO:28-31, in view of the teaching of Herbert, Bowie et al, and Roger et al, supra, and further in view of the unpredictability of protein chemistry, as taught by Burgess et al, Lazar et al, Tao et al, Gillies et al, all of record. Thus based on the teaching in the art and in the specification, one cannot predict that additional

sequences, with unknown structure, attached to SEQ ID NO:28-31 would not change the conformation of the epitopes.

The specification fails to disclose sufficient guidance and objective evidence as to the linear and/or three-dimensional conformation of the polypeptide comprising SEQ ID NO:28-31. The specification has not taught what the structure is for the sequences attached to the defined fragment, SEQ ID NO:28-31 The specification has not taught what the conformation of the claimed numerous polypeptide comprising SEQ ID NO:28-31 is.

All other rejections are withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, CHRISTINA CHAN can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS
May 13, 2004

SUSAN UNGAR, PH.D
PRIMARY EXAMINER